The Problem of Lupus Erythematosus

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SUMMARY

Lupus erythematosus is a challenging disease. Progress in our knowledge of it will come only from intensive research, but in the meantime the practicing dermatologist must be on the alert to make his own observations, to follow current literature carefully and welcome new discoveries from any reliable source. The disease is not the sole property of dermatology; we should rejoice at the interest of pathologists and internists in this condition and work closely with them.

LUPUS erythematosus is common in America, and though its clinical features are well known, the basic knowledge of either the acute or chronic forms has advanced but little since the disorder was first described late in the nineteenth century. The cause of the disease remains a mystery and an effective treatment has not been discovered. It is pertinent, then, briefly to review and reevaluate the known facts and to speculate on the direction in which to seek new knowledge.

Lupus erythematosus was described by such early dermatologists as von Hebra, Biett and Cazenave. A total of about 15 synonyms for the condition has appeared in the literature, all of which implied an erythematous lesion which progressed centrifugally and healed with a central atrophic scar. The acute form was likened to erysipelas by Kaposi. The chronic form was noted to have a number of morphologic variations, each of which was designated by a modifying adjective, while the severity of the systemic reaction was the basis for classifying the types of the acute variety.

The amount and degree of erythema, hyperkeratosis and atrophy were utilized in classification of the chronic form, while the presence or absence of fever was the chief criterion in appraising the acute form. Localization or dissemination of the lesions was also thought to be significant in the latter, not so much because of the number of lesions as because of the fact that systemic symptoms accompanied extensive eruptions. The well-known signs which differentiated acute from chronic inflammation in general were applied to the lesions of lupus erythematosus and were sufficient to make a quick distinction.

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The following scheme of classification has been found valuable:

Form	*Type of Lesion*	
1. Chronic lupus erythematosus	1. Localized	a. Erythematous or congestive b. Edematous c. Papular d. Tumidus e. Hypertrophic verrucous f. Telangiectatic
	2. Disseminated	May have any of above characteristics — either one type or mixture
2. Sub-acute lupus erythematosus	1. Localized 2. Disseminated	
3. Acute lupus erythematosus	1. Disseminated accompanied by A. High fever (severe) B. Low fever (moderately severe) C. Absence of fever (mild)	

EVOLUTION

There is no characteristic primary lesion for any form of lupus erythematosus; what is looked upon as an early or first sign is in reality accentuation of an uncharacteristic beginning. Slight erythema and edema are probably the beginning phase of a lesion which soon assumes a diagnostic character, but a clinical diagnosis cannot be certain until erythema, follicular dilation, hyperkeratosis and even atrophy become apparent. Further evolution often reveals infiltration, telangiectasia and pigmentation. The variance in the degree of the characteristics mentioned determines the type of lesion, while the size, number and distribution of the lesions assist in evaluating the patient's condition.

All lesions of lupus erythematosus progress peripherally or centrifugally; thus the resulting outline is round, oval, or gyrate. Lesions may coalesce so that the outline is a composite of two or more lesions. The border and the zone just outside of the border is the more acute and newer portion of the lesion, hence is brighter in color. The actual border may have a darker tint while the center, especially if atrophy and scaling are present, has a gray appearance. The zones of a discoid lesion indicate the stage of the pathologic process. The appearance of the lesion is dependent upon the degree of hyperkeratosis and the depth is determined by the amount of edema and infiltrate which develops. It is not necessary to reiterate the variations in the types of chronic or fixed lesions. The type of lesion has no prognostic value but the behavior of the lesions has. As a rule the presence of a small number of lesions which progress slowly and become atrophic early indicates that the patient has the power to control

the disease, whereas continued appearance of numerous new lesions on various parts of the body, particularly if they appear on areas other than the face, indicates poor resistance. Purely edematous lesions which enlarge rapidly direct attention to the general condition of the patient and may indicate danger of acute dissemination.

LOCALIZATION

All types of lesions of lupus erythematosus have a predilection for exposed parts of the body—regions which are subject to the effects of light, heat, cold and minor trauma. The nose, cheeks, chin, forehead, sides of the neck, the ears, upper sternal portion of the chest, intrascapular region, and back of the hands are areas involved most frequently in about the order mentioned. The so-called seborrheic areas are the sites of predilection for chronic lupus erythematosus. Strangely, the scalp is also a common location for lesions. The lips and buccal mucosa may be involved in a chronic case, while in an acute disseminated case, involvement of all visible mucous membranes is the rule. There is a rare, widely disseminated form of lupus erythematosus which has the appearance of psoriasis and a similar distribution.

ETIOLOGIC FACTORS

The fact that the lesions of lupus erythematosus occur on areas of the body exposed to light has emphasized what may be an erroneous concept; namely, that patients with lupus erythematosus are sensitive to light. Many such patients have definitely stated that exposure to sunlight aggravated or even precipitated the lesions. On the other hand other patients with chronic lupus erythematosus are outdoor workers, frequent bathing beaches, or indulge in outdoor sports, without any exacerbation of the condition. The first exposures in the spring in a northern climate seem to affect the patients most, but they soon become accustomed to the sunlight. It is true that histories of patients with the acute, disseminated form of the disease often reveal that the attack began with a prolonged, unaccustomed exposure to sunlight, but many acute cases occur without such exposure. An exposure to winter sunlight rarely precipitates an attack.

Porphyrin metabolism, exposures to and experiments with various wave lengths of the spectrum and the relationship of the condition to liver function, diet, and state of nutrition are just a few of the factors about which we need to know a great deal more before we can state unreservedly that the lesions or attacks of lupus erythematosus are aggravated by sunlight. It has been observed that the areas which are commonly attacked by lupus erythematosus have a tendency to local asphyxia under the influence of cold. This leads to a query regarding the ability of the blood vessels to react in patients with lupus erythematosus. Patients having the so-called chilblain type of circulation often have a tendency to arthritis. As in erythema multiforme, there seems to be a vague connection between these occurrences in lupus erythematosus, but there is no positive proof that the diseases belong to the same group.

A striking observation is the distinct increase in the incidence of lupus erythematosus in the months of spring and early summer. Freund[2] studied the general factors that influence lupus erythematosus. He critically examined the protocols of 383 female and 124 male patients seen in Arndt's clinic in Berlin and noted that the greatest number of cases occurred in the period March through July, while December was the month of lowest incidence.

Lupus erythematosus occurs most frequently from the second through the fourth decade. Few cases are seen in the first decade and the same holds true for people past 70 years of age. In my experience the few cases in children under 10 have all been acute or subacute in type. One child, five years of age, had a severe acute attack, the child hovering between life and death for many months. He was not seen again until he was 22 years of age. At that time he had an extensive but chronic form of lupus erythematosus.

Other climatic factors such as heat, cold, humidity and moisture may be of some importance, for lupus erythematosus is more common in the temperate zone than in the tropics. It appears to me, however, that, although external factors play some role in the localization and occurrence of this disease, they do not furnish much information as to its cause. Spitzer stated that season and climate exert a decided influence on the occurrence of lupus erythematosus, but whether this was in the negative or positive sense could not be stated. In Western Europe and America, cases of lupus erythematosus constitute no more than one per cent of the total number of skin cases in statistics collected by a number of dermatologists. There is considerable variation in the figures, some being as low as 0.3 per cent while none are over one per cent. It is interesting to note that in Breslau, lupus vulgaris occurred about four times as often as lupus erythematosus. Ehrmann and Falkenstein,[1] in 1922, carefully reviewed cases of lupus erythematosus observed in Austria. They remarked that about one quarter of all such cases recorded in Austria occurred in Vienna, and that there had been a great increase in the incidence of the disease both in its chronic and acute forms in the previous decade.

According to most observers the ratio of females to males with lupus erythematosus is about 3:1. This has led to speculation regarding an etiologic endocrine factor and, since the acute form is rarely encountered in males, drastic treatment directed at ovarian function has been undertaken in this form.

Pregnancy has an influence on some cases of lupus erythematosus; observers believe that it is a bad one in acute cases and advise therapeutic abortion. I observed one patient with acute lupus erythematosus, which began in the sixth month of pregnancy. Although extremely ill, the patient decided against an

abortion, was delivered of a healthy child and recovered from the lupus erythematosus. She has been observed for 12 years and, although she has some chronic lesions on her cheeks, she has remained quite well. That some female patients with acute lupus erythematosus have been benefited by temporary suppression of ovarian function or by radical castration cannot be denied, but the procedure has not been successful in a large enough percentage of patients to warrant advocating it. The mechanism which brings about improvement when it occurs in such cases is not clear. I observed one female patient with extensive chronic discoid lupus erythematosus through two pregnancies. Each time the active lesions entirely disappeared, but new lesions developed about four months after delivery. Likewise, irradiation of gland-bearing areas, as advocated by Gennerich and practiced at one time by Goeckerman, has not been successful sufficiently often to be accepted as a standard procedure.

The cause of the disease remains obscure. At one time observers looked upon the various forms of lupus as forming a family of conditions. After the tubercle bacillus was discovered to be the cause of lupus vulgaris, it was assumed also to be the cause of lupus erythematosus. All the well-known methods of trying to establish a tuberculous cause were applied to this condition. In searching for the bacilli, animal inoculations and blood cultures were made, tissue extracts from excised lesions were searched for a tuberculin-like substance. Thorough postmortem examinations were made, especially in acute cases, and it was attempted to associate lupus erythematosus with lesions said to be tuberculous, such as tuberculosis adenitis and erythema induratum. In the voluminous literature on lupus erythematosus, some so-called proofs of tuberculous origin are to be found. Many observers, for example Keil, have avowed tuberculosis as the cause of lupus erythematosus. The subject must not be dismissed as closed, for some patients with the acute form of this disease have shown active tuberculosis at autopsy.

The pathologic studies of Klemperer and coworkers[3] have drawn attention away from the alterations that one would expect in tuberculosis; namely infiltration and necrosis, and have called attention to alterations in the collogen system. The widespread presence of these changes, especially in the skin, heart, kidneys and blood vessels, is in keeping with the generalized nature of the acute form of the disease, but still does not point out a cause.

PATHOLOGY

The pathologic changes of chronic discoid lupus erythematosus and the cutaneous changes in the acute form are certainly similar and make one unwilling to separate the two conditions into different diseases. This similarity, together with the fact that chronic cases have been known to become acute and, more rarely, that chronic lesions have persisted after a long, serious, acute attack, cannot be ignored. The great discrepancy between the severity of the two forms is hard to reconcile. How the chronic form may remain so inert and symptomless, while the acute is so severe and usually fatal, makes acceptance of unity almost insurmountable. The only common ground is a microscopic study of actual lesions. The pathologic changes of the more fixed type offer opportunity for extensive and thorough study. I have found it advisable to completely excise small, new lesions and have them cut serially in order to observe early changes. I have also excised some lesions which were in the erythematous or congestive stage. These studies, added to the examination of a great many routine excisions from chronic discoid lesions, have made it possible at least to describe the histologic differences observed.

The pathologic changes of the fixed type of lupus erythematosus are made up of three distinct processes: First, a vascular or perivascular disturbance, followed by edema and subsequent damage of connective tissue, followed by an infiltration and finally, epidermal and follicular alterations. The changes will depend, to be sure, to some degree on the type of lesion under consideration, and it must be emphasized that a uniform picture for lupus erythematosus does not exist.

The initial lesion seems to be a rather extensive, but irregular, dilation of the small blood vessels, noted particularly in the upper portion of the cutis. Edema goes hand in hand with this, separating the connective tissues. The edema has a very sharp line of demarcation in a horizontal plane and is most marked in the papillary portion of the cutis. The cutis below the horizontal boundary appears to be quite normal except for small foci of infiltrating small leukocytes. The epidermis may remain unaffected at first or show a variety of secondary changes. In the erythematous, transient type of lesion the changes are so slight and mostly edematous that it can readily be understood why such lesions may disappear without enough damage having been imparted to either the connective tissues or the epidermis to leave a scar. In the far more common type of chronic lesion, the vascular dilatation, edema and infiltrate become more marked, especially the infiltrate, and changes in the epidermis and connective tissues are severe enough to cause irreparable damage and therefore scar formation.

I am convinced that the papillary edema with a sharp horizontal boundary is an important first change. The infiltrate accumulates in various amounts forming masses of different shapes. Some are globular, appearing as round areas in the section, separated from each other, when deep, by nearly normal elements. In other specimens, the infiltrate seems to form large cubes so that the mass appears to be a square block in the section, often pushing up to or contiguous to the flattened epidermis. This is a common finding in an old discoid lesion. The infiltrate consists of small, darkly stained closely packed leukocytes. The cells are uniform in type, with an occasional larger, paler cell seen. Other

types of cells, such as plasma, mast or giant cells are conspicuous by their absence. Such cells have been seen by some students of the subject but they certainly are not a common finding. Accumulations of red blood corpuscles are often seen in the infiltrate. The edema and infiltrate affect the connective tissue, or possibly the noxa of lupus erythematosus does so first. As aforementioned the collogen, especially in the papillary portion of the cutis, changes its affinity for the common dyes early and it appears swollen, drenched and pale and there is a decided separation with the formation of spaces. In the infiltrated areas the collogen completely disappears; the elastic fibers also are lost only to appear at the periphery of the infiltrate and in the non-infiltrated areas as heavy, broken bits, looking as though they had been stretched, torn and then snapped into condensed thick segments. This destruction of the connective tissue and the epidermal thinning account for the terminal atrophy.

The epidermis, disturbed by the edema, infiltrate and, I believe, change in cohesion, shows a variety of changes. The basal layer shows the effect of the underlying edema early. The individual cells become vacuolated and the nuclei, shrunken and misshaped, appear to float in the altered cells. The change is much like that seen in a mild dermatitis. The cell boundaries remain distinct, and although there must be a decided physiologic change in the cell, possibly a necrobiosis, I do not believe that there is true necrosis, for there is no ulceration. The basal outline changes, usually into a straight line. The epidermis is reduced to a few layers and there is some degree of hyperkeratosis. All the epidermal changes are not uniform; more marked in some areas than in others. The epidermal appendages may be lost, remnants being noticed in the dense infiltrate, or the epidermal change may be seen especially in the sebaceous follicle. Dilation and hyperkeratosis are most striking and the follicle may contain cornified debris.

To summarize: The pathologic changes of chronic lupus erythematosus are characterized chiefly by a variability of the degree of edema, infiltrate and epidermal atrophy. The process takes place in a fairly orderly manner in about the order mentioned. Although this is fairly diagnostic, one must constantly keep the process as a whole in mind and not base his opinion on too rigid a concept. In some instances, chronic lupus erythematosus may be readily recognized microscopically; in others the pathologic changes may be very hard to identify with the disease. The type and size of the lesion and the particular zone from which the tissue was taken should be known. It would be a mistake to state that the findings are pathognomonic.

No reports were found in the literature describing any findings in those organs commonly involved in the acute form of the disease in autopsies of patients who had chronic lupus erythematosus and died from some other cause. This constitutes a deficiency in our knowledge and I believe such studies would be of immense value in correlating the two extremes of this disease.

The microscopic anatomy of the skin in acute disseminated lupus erythematosus is well-known. Edema, infiltrate and atrophy are encountered in the skin of chronic discoid lupus erythematosus and in the acute form the process is similar but, as to be expected, much more rapid and intense. Edema and necrosis are the outstanding features. The edema again is in the upper portion of the cutis but so intense that bullae are often formed. The epidermis is separated from the cutis and it degenerates rapidly, forming crusts. Hemorrhage is often associated with the edema, and erythrocytes are seen in the infiltrate, which is not as dense or plentiful as in the chronic type. There is a decided similarity between the cutaneous pathology of the acute disseminated type and the chronic form, the outstanding difference being the intensity of the process in the former. Microscopic examination of the skin is of diagnostic help in obscure cases in which lupus erythematosus is suspected and, when all factors have been considered, is often confirmative.

For the pathologic findings in the internal organs we are indebted largely to the work of the Mount Sinai (New York) group. There, under the inspiration of Libman, Baehr, and Klemperer, our knowledge of this puzzling disease has been greatly advanced and the direction for further investigations has been suggested. I shall not review their many contributions but merely quote from Klemperer's most recent article. He states: "I believe that the present state of information permits us to conclude that acute lupus erythematosus is defined anatomically as a disease characterized by a fundamental alteration of the collogenous portions of the connective tissues. The exact nature of their alteration must be determined by investigation with the methods of histology, biochemistry and biophysics."

The internal organs most often involved are the heart, kidneys, spleen and serous membranes. The morbid anatomy includes fibrinoid metamorphosis of the collogenous fibers and local necrosis. The interpretation of the details of these findings are beyond my present knowledge and the reasons for their occurrence are still in a state of conjecture. Although the process suggests an infection, painstaking studies have not disclosed a bacterial cause. The leukopenia often present, the anemia, and more recently a new type of cellular inclusion found in marrow preparations, all point to an agent which affects the hemopoietic system.

Analysis of the findings in study of the cutaneous pathologic changes allows certain conclusions to be drawn. From the more or less constant picture seen, it would seem that tuberculosis may be excluded as the cause of the disease. The edema and infiltrate in themselves are comparable to pathologic changes provoked by infections and also by chemicals which are carried by the blood stream, such as bromine and arsphenamine. Since the chemical and microscopic findings in lupus erythematosus are so con-

stant and characteristic, it would seem logical that we are dealing with an entity. The widespread damage in the acute form points to a blood-borne cause, and even in the fixed variety the pathologic process seems to have its origin from within.

The evidence that allergy plays a role in acute lupus erythematosus is not convincing. The endocrine factors, though startling, are not explanatory. The grave systemic nature of the disease is terrifying and the postmorten findings do not explain the death of the patient. Pathologic studies in themselves have about exhausted the searches for the cause of lupus erythematosus. The newer enzyme studies, a search for chemical and physical agents which may lay the groundwork for the pathologic process, as well as many other researches are necessary. We may have to wait for new methods of research not yet discovered, before the cause of lupus erythematosus can be found.

I shall not discuss diagnosis in this article. Chronic lupus erythematosus does not offer a great diagnostic problem. The differentiation between the acute disseminated form and dermatomyositis is at times very difficult and the conditions have much in common. Microscopic examination of excised muscle is positive in only approximately 20 per cent of cases of dermatomyositis and an adequate series of such excisions in acute lupus erythematosus patients is needed for comparison.

TREATMENT

There is no specific treatment for any form of lupus erythematosus. In fact, one might better state that there is no successful treatment for lupus erythematosus. In the chronic form, disappearance of the lesion or early scarring is the object of therapy. Localized lesions expected to disappear without a trace are few in number and of the congestive type. For them the internal use of gold or bismuth salts is usually employed, but since this type of lesion often spontaneously disappears it is doubtful if any therapy should be employed. External applications in this form of the disease should be avoided, for even the mildest ointment may cause irritation. No physical therapy is indicated.

In the more chronic discoid lesions, gold and bismuth salts are often used. It is doubtful if any benefit is derived from this treatment. There is often some initial improvement, but on the whole the results are disappointing. Such lesions will end in scars; hence to hasten scarring by the use of carbon dioxide snow seems sensible and is my treatment of choice. Protection from the sun's rays by means of chemicals incorporated in ointment bases helps some patients. Quinine is supposed to do likewise. Vitamin E and para-amino-benzoic acid or its sodium salt have recently been advocated. All in all, I am skeptical about the known remedies for chronic discoid lupus erythematosus, but I feel receptive to any new procedure that is worthy of trial.

The object of treatment in the acute form is to save the life of the patient. This calls for hospital treatment employing all the supportive measures known. Transfusions, intravenous fluids and feedings, judicious use of opiates, not sedatives, and the optimum degree of care on the part of the resident and nursing staff yield some satisfying results. The sulfonamides, penicillin, and streptomycin have not been effective. In fact, the sulfonamides may be contraindicated because some patients are made worse by their use. The treatment of acute disseminated lupus erythematosus is extremely disappointing and, although temporary improvement is noted and even rather long remissions occasionally are brought about, ultimate defeat with death of the patient is the most common outcome.

A large percentage of patients with chronic lupus erythematosus suffer little from their malady. The cosmetic appearance is to be deplored and cancer in lupo must be kept in mind, but dissemination is extremely rare.

The patient who has had evanescent facial lesions presents a special problem. Is he candidate for the acute form of the disease? In such cases, I believe that dissemination may be provoked and has been provoked by the use of ultraviolet radiation. One might speculate that dissemination was imminent and the therapy merely hastened the extension. However, it is difficult to explain the coincidence and I believe that the patient with lesions of the congestive type should be guarded from any possible therapeutic accident.

Patients with widely spread chronic psoriasiform lupus erythematosus are rare but present a great therapeutic problem. They are semi-invalids and do not respond to any known measures. Supportive measures, liver injections, local emollients and constant surveillance are the only suggestions.

Occurrence of periungual lesions is looked upon as a grave prognostic sign in our clinic. Edema, actual swelling and exudate with crust formation also are unfavorable changes in a fixed lesion.

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